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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/209,125	12/10/1998	JAYASHREE AIYAR	PHM.70293-US	9087

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/209,125	AIYAR ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 25, 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5, 8, and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment A*.

DETAILED ACTION

Formal Matters

Claims 1 and 8 were amended in the communication dated June 25, 2001. Currently, claims 1-5, 8 and 9 are pending and under consideration. The finality of the last Office action is withdrawn, and new grounds of rejection are set forth below.

Claim Rejections Withdrawn

The rejection of claims 1-5, 8 and 9 under 112, second paragraph, as being indefinite for reciting the term "biologically active" or "biologically-effective" are withdrawn in view of Applicant's amendments.

Claim Rejections - 35 USC § 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the claim is directed to a host cell. Applicants are not in possession of any and all host cells. In the instant case, a host cell can refer to one that is still in a living being.

Claims 1-5, 8 and 9 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby.

The instant application does not disclose the significance of the biological role of this protein. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001. The specification states that the present invention is directed to a novel treatment of a patient in need of such treatment for a condition which is mediated by a potassium channel, or for a condition which is mediated by the biological activity of human potassium channel, or by neurophysiology, comprising administration of a potassium channel modulating compound (p. 6, lines 20-29). The claimed polynucleotide is not supported by either a specific and substantial utility, or a well-established utility, because the specification fails to disclose the nexus between any particular disease state and an altered level or form of the claimed polypeptides and further any specific treatment(s) for said disease. See *Brenner v. Manson,* 148 USPQ 689 (U.S. Supreme Court, 1966), in which a novel compound which was structurally analogous to other compounds which were known to

possess anticancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a polynucleotide (including SEQ ID NO: 2) that encodes a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport, the complement of said polynucleotide, associated expression vectors and host cells, and methods for producing said polypeptide and for producing cells which express said polypeptide. Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO: 3, the instant invention is incomplete. In the absence of knowledge of the biological significance of this protein in any specific disease state, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances

that inhibit its activity is clearly to use it as the object of further research, which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for SEQ ID NO: 3, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 1-5, 8 and 9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, assuming arguendo, that a sufficient utility is found for the claimed polynucleotide and polypeptide, claims 1, 3, 5, 8 and 9 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record in the office action dated February 27, 2001 (p.4, line 15 – p.8, line 12). Further, claim 2 and 4 are rejected for the reasons stated in said office action. In addition, the current pending claims are rejected because there is no disclosed function recited in the claims for the fragments of SEQ ID NO: 3.

In the communication dated June 25, 2001, Applicant argues that the proposed amended claims now recite a specific biological activity that the polypeptide(s) of the invention must possess. Applicant has also pointed out that the specification (page 19, line 15 onwards), discloses deletion, insertion, substitution and truncation variants and

teaches what amino acid substitutions (particularly conservative amino acid substitutions) may be made and notes that computer programs well known in the art can be used to predict what amino acid substitutions can be made without substantially altering the biological activity of the protein.

Applicant's argument has been fully considered and is not found to be persuasive. The claims are drawn to a polynucleotide (including SEQ ID NO: 2) that encodes a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport, the complement of said polynucleotide, associated expression vectors and host cells, and methods for said polypeptide and for producing cells which express said polypeptide.

There is no guidance provided in the specification as to how one of ordinary skill in the art would make and use the polypeptides of the current invention having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport other than those exemplified in the specification. Applicant argues that it would require routine experimentation to follow the guidelines set forth in the specification to prepare said proteins or variants. However, even at a 85% homology, SEQ ID NO: 3 is 854 amino acids long, thus mutations could be introduced at up to ca. 128 amino acids, and each possible mutation is chosen from 20 possible amino acids. These claims encompass a very large number of possible members of the genus (128^{20} possible members, not including deletion mutants). Additionally, there is insufficient guidance provided to

indicate which amino acid residues are necessary for the polypeptide function of allowing transmembrane potassium ion flow and/or transport.

As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, de1ta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype, thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Additionally, Yan et al. teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to

another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass a polynucleotide (including SEQ ID NO: 2) that encodes a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport, the complement of said polynucleotide, associated expression vectors and host cells, and methods for said polypeptide and for producing cells which express said polypeptide, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention. Given the large number of possible species encompassed by the claims, and the insufficient guidance provided in the specification as to the critical residues necessary for protein function, it would require undue experimentation of one of skill in the art to make and use the claimed invention.

Claims 1, 3, 5, 8 and 9 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record in the office action dated February 27, 2001 (p.8, line 15 – p.10, line 19). Further, claims 2 and 4 are newly rejected for the reasons stated in said office action. In addition, the current pending claims are rejected because there is no disclosed function recited in the claims for the fragments of SEQ ID NO: 3.

The rejection argues that while the specification and the art provides adequate written description for a polynucleotide of SEQ ID NO: 2 that encodes a polypeptide of SEQ ID NO: 3, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport and methods reciting said polynucleotide and said polypeptide, the specification fails to adequately describe a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport, a polynucleotide that encodes said polypeptide, the complement of said polynucleotide, associated expression vectors and host cells, and methods for producing said polypeptide and for producing cells which express said polypeptide.

The skilled artisan cannot envision all of the amino acid sequences that have at least 85% identity with SEQ ID NO: 3 or the polynucleotides that encode said polypeptides or the fragments thereof that have no disclosed function, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Only a polynucleotide of SEQ ID NO: 2 that encodes a polypeptide of SEQ ID NO: 3, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport and methods reciting said

polynucleotide and said polypeptide meet the written description provision of 35 U.S.C. § 112, first paragraph.

Applicant has pointed out that the specification (page 19, line 15 onwards), discloses deletion, insertion, substitution and truncation variants and teaches what amino acid substitutions (particularly conservative amino acid substitutions) may be made and notes that computer programs well known in the art can be used to predict what amino acid substitutions can be made without substantially altering the biological activity of the protein. Applicant argues that the claims are supported by adequate written description with respect to claims that recite amino acid sequence identity and associated biological activity. Applicant argues that they have cloned, sequenced, characterized and thus identified a novel brain derived potassium channel and that it is well established in the art that truncated variants of many proteins can be made without substantially altering the biological activity of the protein. Additionally, whilst it is acknowledged that that a single amino acid substitution at a particular location can potentially destroy a particular biological activity, it is also well established that most amino acids can be changed without substantially altering the particular biological activity at issue.

Applicant argues that the specification contains an adequate written description of the claimed subject matter because the claims contain a function (allowing transmembrane potassium ion flow and/or transport) and a structural limitation (85% homology with SEQ ID NO: 3). However, in University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997), the court held that one of two elements may satisfy

a genus of cDNAs, i.e. i) a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or; ii) a recitation of structural features common to members of the genus, which features constitute a substantial protein of the genus. In the instant case, the first element is not met because only a cDNA encoding SEQ ID NO: 3 is disclosed. The second element requires structural features common to members of the genus, however, in the instant disclosures, insufficient guidance is provided as to which are the critical residues necessary for the claimed protein function of allowing transmembrane potassium ion flow and/or transport. Even at a 85% homology, SEQ ID NO: 3 is 854 amino acids long, thus mutations could be introduced at up to ca. 128 amino acids, and each possible mutation is chosen from 20 possible amino acids. These claims encompass a very large number of possible members of the genus (128^{20} possible members, not including deletion mutants).

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell, does not reasonably provide enablement for any host cell.

The claim is drawn to a host cell transformed with the expression vector that comprises a purified polynucleotide that encodes the proteins of the current invention. In the specification (p. 35, lines 18-27), host cells are defined as being either eukaryotic or prokaryotic and include yeast, mammalian cells including but not limited to cell lines of human, bovine, porcine, monkey and rodent origin, and insect cells including but not limited to Drosophila and silkworm derived cell lines. Also, examples of cell lines from

mammalian species are disclosed. Further, in the specification (p. 36, lines 4-18), the incorporation of the nucleic acid molecule into the host cell is described, as well as the subsequent maintenance of said host cell for expression and identification of the encoded protein product. The conditions described by the specification encompass *in vitro* methods; however, there is no guidance provided in the specification as to how one of ordinary skill in the art would practice these methods *in vivo*.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a limitation for the source of said host cell, e.g. isolation of said host cell. Since detailed information regarding the structural and functional requirements of the host cell are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass a host cell, it would require undue experimentation of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the phrase "as depicted in" SEQ ID NO: 2. The phrase "as depicted in" is vague and indefinite because it is not clear whether the term is directed to the full-length nucleic

acid of SEQ ID NO: 2, or to a portion of SEQ ID NO: 2. The metes and bounds of the claim thus cannot be ascertained. If the claim language was amended to include the phrase "of" SEQ ID NO: 2 the rejection would be obviated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 1, 3, 5, and 8 under 35 U.S.C. 102b as anticipated by Yokoyama et al. (1996) are maintained for reasons of record in the office action dated February 27, 2001 (p.11 – p.13, line 2).

In the communication dated June 25, 2001, Applicant argues that the polypeptide of Yokoyama is only 393 amino acid residues long and actually represents a short splice variant" of the KCNQZ gene. Although the Yokoyama polypeptide may possess the ability to bind another subunit, ligand or co-factor, it is incapable of functioning as a potassium channel (allowing transmembrane potassium ion transport and/or flow). The

Yokoyama polypeptide is missing the C-terminal tail of the polypeptide of the present invention and the Applicant has found that the Yokoyama polypeptide is not capable of functioning as a potassium channel. The amended claims require the polypeptide to be capable of allowing transmembrane potassium ion transport and/or flow.

Applicant's argument has been fully considered and is not found to be persuasive. The current claims are drawn to a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow and/or transport. There is no functional limitation for the polypeptide fragment recited by the claims. As stated by Applicant, the polypeptide of Yokoyama is a short splice variant (i.e., fragment) of the polypeptide of the instant invention. Therefore, it is irrelevant that the polypeptide fragment of Yokoyama does not posses the recited functional limitation of the full-length polypeptide of the instant invention and thus anticipates the claims on the instant invention. Since the Yokoyama reference teaches all of the elements of the claims, claims 1, 3, 5, and 8 stand rejected under 35 U.S.C. 102b.

Claim 4 is rejected under 35 U.S.C. 102(e) as being anticipated by US PGPub 2003/0165874 A1 to Leppert *et al.* The claims is directed to an oligonucleotide comprising a complement of the polynucleotide of claim 2, wherein the polynucleotide sequence comprises the sequence as depicted in SEQ ID NO: 2.

SEQ ID NO: 1 of the '874 document teaches an oligonucleotide that has 99.9% local similarity to Applicant's SEQ ID NO: 2 (see attached sequence alignment) and is

thus a complement of Applicant's SEQ ID NO: 2. Since the document teaches all the elements of the claim, claim 2 is anticipated by US PGPub 2003/0165874 A1 to Leppert *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claim 9 under 35 U.S.C. 103a as unpatentable over Yokoyama et al. (1996) in view of WO 96/03415 to Li et al. are maintained for reasons of record in the office action dated February 27, 2001 (p.13, line 3 – p.16, line 4).

In the communication dated June 25, 2001, Applicant argues that in view of the fact that the protein of Yokoyama et al. does not possess the requisite biological activity (potassium ion transport) recited in the amended claim, the claimed invention cannot then be considered obvious over Yokoyama et al. in combination with Li et al.

Applicant's argument has been fully considered and is not found to be persuasive. As outlined above, the current claims are drawn to methods reciting a polypeptide having at least 85% homology with SEQ ID NO: 3 or a fragment thereof, said polypeptide possessing the ability to allow transmembrane potassium ion flow

and/or transport. Again, there is no functional limitation for the polypeptide fragment recited by the claims. The polypeptide of Yokoyama is a short splice variant (i.e., fragment) of the polypeptide of the instant invention; therefore, it is irrelevant that said fragment of Yokoyama does not posses the recited functional limitation of the full-length polypeptide of the instant invention and thus anticipates the claims on the instant invention. Since the Yokoyama reference anticipates the elements of the claim, claim 9 stands rejected under 35 U.S.C. 103a as being unpatentable over Yokoyama et al. (1996) in view of WO 96/03415 to Li et al.

Conclusion

No claims are allowed.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 8:30AM to 5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph. D.
Patent Examiner
Art Unit 1649
August 29, 2005

JOSEPH MURPHY
PATENT EXAMINER